

CLAIMS:

1. A pharmaceutical composition comprising a dopamine D₁ receptor agonist; a dopamine D₂ receptor antagonist; and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof, wherein the amount of the dopamine D₁ receptor agonist and the amount of the dopamine D₂ receptor antagonist are each effective for treating a patient at risk of developing or having a neurological, psychotic, or psychiatric disorder.
2. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist is a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzazepines, chromenoisoquinolines, naphthoisooquinolines, analogs and derivatives thereof, pharmaceutically acceptable salts thereof, and combinations thereof.
3. The pharmaceutical composition of claim 1 wherein the neurological, psychotic, or psychiatric disorder is selected from the group consisting of schizophrenia, schizophreniform disorders, schizoaffective disorders, cognitive disorders, memory disorders, autism, Alzheimer's disease, dementia, bipolar disorder, depression in combination with psychotic episodes, and other disorders that include a psychosis.
4. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist is a full agonist.
5. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist is selective for a dopamine D₁ receptor subtype.
6. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist exhibits activity at both the dopamine D₁ and D₂ receptor subtypes.
7. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist is about equally selective for the dopamine D₁ and D₂ receptor subtypes.
8. The pharmaceutical composition of claim 1 wherein the dopamine D₁ receptor agonist exhibits activity at both the dopamine D₁ and D₂

receptor subtypes, and the dopamine D₁ receptor agonist exhibits greater activity at the dopamine D₁ receptor subtype

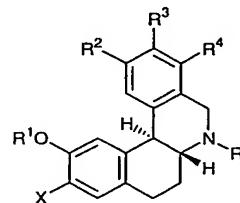
9. The pharmaceutical composition of claim 1 wherein the
dopamine D₂ receptor antagonist does not exhibit significant binding at the dopamine
5 D₁ receptor.

10. The pharmaceutical composition of claim 1 wherein the dopamine D₂ receptor antagonist does not exhibit significant functional activity at the dopamine D₁ receptor.

11. The pharmaceutical composition of claim 1 wherein the
10 dopamine D₂ receptor antagonist does not exhibit significant agonist activity at the
dopamine D₁ receptor.

12. The pharmaceutical composition of claim 1 wherein the dopamine D₂ receptor antagonist does not exhibit significant antagonist activity at the dopamine D₁ receptor

15 13. The pharmaceutical composition of claim 1 wherein the dopamine receptor agonist is a compound of the formula



wherein

R is hydrogen or C₁-C₄ alkyl;

20 R¹ is hydrogen, acyl, benzoyl, pivaloyl, an optionally substituted phenyl protecting group;

X is hydrogen, fluoro, chloro, bromo, iodo; or X is a group having the formula -OR⁵ wherein R⁵ is hydrogen, C₁-C₄ alkyl, acyl, benzoyl, pivaloyl, an optionally substituted phenyl protecting group; or the groups R¹ and R⁵ are taken together to form a divalent radical having the formula -CH₂- or -(CH₂)₂-; and

R^2 , R^3 , and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, phenyl, fluoro, chloro, bromo, iodo, and a group $-OR^6$ wherein R^6 is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

or a pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of claim 13 wherein the compound is racemic.

15. The pharmaceutical composition of claim 13 wherein at least 5 one of the groups R², R³, and R⁴ is other than hydrogen.

16. The pharmaceutical composition of claim 13 wherein R is hydrogen or methyl; R¹ is hydrogen; X is hydrogen, bromo, or -OR², and R² is hydrogen.

17. The pharmaceutical composition of claim 13 wherein R is 10 methyl; and X is bromo.

18. The pharmaceutical composition of claim 13 wherein R is methyl; and X is hydrogen.

19. The pharmaceutical composition of claim 13 wherein at least one of the groups R², R³, and R⁴ is methyl.

15 20. The pharmaceutical composition of claim 13 wherein X is hydroxy.

21. The pharmaceutical composition of claim 13 wherein R is hydrogen.

22. The pharmaceutical composition of claim 13 wherein R is C₁-20 C₄ alkyl.

23. The pharmaceutical composition of claim 13 wherein R is methyl.

24. The pharmaceutical composition of claim 13 wherein R is n-propyl.

25 25. The pharmaceutical composition of claim 13 wherein R is hydrogen; R² is methyl; R³ and R⁴ are each hydrogen; R¹ is hydrogen; and X is hydroxy.

26. The pharmaceutical composition of claim 13 wherein R and R¹ are each hydrogen; X is hydroxy; R³ is methyl; and R² and R⁴ are each hydrogen.

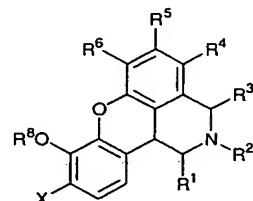
30 27. The pharmaceutical composition of claim 13 wherein R and R¹ are each hydrogen; X is hydroxy; R⁴ is methyl; and R² and R³ are each hydrogen.

28. The pharmaceutical composition of claim 13 wherein the compound is DAR-110.

29. The pharmaceutical composition of claim 13 wherein the compound has a half-life in the range from about 30 minutes to about 3 hours.

30. The pharmaceutical composition of claim 1 wherein the dopamine receptor agonist is a compound of the formula

5



wherein

R^1 , R^2 , and R^3 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl and C_2 - C_4 alkenyl;

R^4 , R^5 , and R^6 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, phenyl, halo, and a group having the formula $-OR$, where R is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

R^8 is hydrogen, C_1 - C_4 alkyl, acyl, or an optionally substituted phenyl protecting group;

X is hydrogen or halo; or X is a group having the formula $-OR^9$, where R^9 is hydrogen, C_1 - C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; or when X is a group having the formula $-OR^9$, R^8 and R^9 are taken together to form a divalent group having the formula $-CH_2-$;

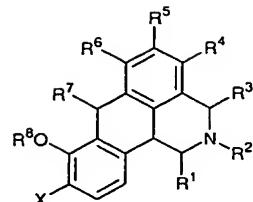
or a pharmaceutically acceptable salt thereof.

20 31. The pharmaceutical composition of claim 30 wherein the compound is racemic.

32. The pharmaceutical composition of claim 30 wherein the compound is optically active having the (+) configuration.

25 33. The pharmaceutical composition of claim 30 wherein at least one of the groups R^4 , R^5 , and R^6 is other than hydrogen.

34. The pharmaceutical composition of claim 1 wherein the dopamine receptor agonist is a compound of the formula



wherein

R^1 , R^2 , and R^3 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, and C_2 - C_4 alkenyl;

5 R^4 , R^5 , and R^6 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, phenyl, halogen, and a group having the formula $-OR$, where R is hydrogen, acyl, benzoyl, pivaloyl, or an optionally substituted phenyl protecting group;

10 R^7 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy, and C_1 - C_4 alkylthio;

R^8 is hydrogen, C_1 - C_4 alkyl, acyl, or an optionally substituted phenyl protecting group; and

X is hydrogen, fluoro, chloro, bromo, or iodo;
 and pharmaceutically acceptable salts thereof.

15 35. The pharmaceutical composition of claim 22 wherein the compound is racemic.

 36. The pharmaceutical composition of claim 22 wherein the compound is optically active having the (+) configuration.

20 37. The pharmaceutical composition of claim 22 wherein at least one of the groups R^4 , R^5 , and R^6 is other than hydrogen.

 38. The pharmaceutical composition of any one of claims 1 through 38 wherein the dopamine D_2 receptor antagonist is an antipsychotic agent.

25 39. The pharmaceutical composition of any one of claims 1 through 38 wherein the dopamine D_2 receptor antagonist is an atypical antipsychotic agent.

 40. The pharmaceutical composition of claim 1 further comprising one or more cholinergic agents, cholinergic agonists, acetylcholine mimetics, acetylcholine esterase inhibitors, or combinations thereof.

41. A method for treating a patient at risk of developing and/or having a neurological, psychotic, and/or psychiatric disorder, said method comprising the step of administering to the patient an effective amount of a composition according to any one of claims 1 through 38.

5 42. A method for treating a patient at risk of developing and/or having a neurological, psychotic, and/or psychiatric disorder, said method comprising the steps of:

10 administering to the patient an effective amount of a full dopamine D₁ receptor agonist, where the agonist is a compound selected from the group consisting of hexahydrobenzophenanthridines, hexahydrothienophenanthridines, phenylbenzodiazepines, chromenoisoquinolines, naphthoisoquinolines, pharmaceutically acceptable salts thereof, and combinations thereof; and

15 administering to the patient an effective amount of a dopamine D₂ receptor antagonist;

20 where the agonist and the antagonist are administered contemporaneously.

25 43. The method of claim 41 wherein the agonist and the antagonist are administered simultaneously.

20 44. The method of claim 41 wherein the agonist and the antagonist are administered in a unitary dosage form.

25 45. The pharmaceutical composition of claim 41 wherein the neurological, psychotic, or psychiatric disorder is selected from the group consisting of schizophrenia, cognitive disorders, memory disorders, autism, Alzheimer's disease, dementia, and combinations thereof.

30 46. The pharmaceutical composition of claim 41 wherein the dopamine D₁ receptor agonist is a full agonist.

47. The pharmaceutical composition of claim 41 wherein the dopamine D₁ receptor agonist is selective for a dopamine D₁ receptor subtype.

30 48. The pharmaceutical composition of claim 41 wherein the dopamine D₁ receptor agonist exhibits activity at both the dopamine D₁ and D₂ receptor subtypes.

49. The pharmaceutical composition of claim 41 wherein the dopamine D₁ receptor agonist is about equally selective for the dopamine D₁ and D₂ receptor subtypes.

50. The pharmaceutical composition of claim 41 wherein the 5 dopamine D₁ receptor agonist exhibits activity at both the dopamine D₁ and D₂ receptor subtypes, and the dopamine D₁ receptor agonist exhibits greater activity at the dopamine D₁ receptor subtype

51. The pharmaceutical composition of claim 41 wherein the 10 dopamine D₂ receptor antagonist does not exhibit significant binding at the dopamine D₁ receptor.

52. The pharmaceutical composition of claim 41 wherein the dopamine D₂ receptor antagonist does not exhibit significant functional activity at the dopamine D₁ receptor.

53. The pharmaceutical composition of claim 41 wherein the 15 dopamine D₂ receptor antagonist does not exhibit significant agonist activity at the dopamine D₁ receptor.

54. The pharmaceutical composition of claim 41 wherein the dopamine D₂ receptor antagonist does not exhibit significant antagonist activity at the dopamine D₁ receptor

20 55. The method of any one of claims 41 through 53 wherein the dopamine D₂ receptor antagonist is an antipsychotic agent.

56. The method of any one of claims 41 through 53 wherein the dopamine D₂ receptor antagonist is an atypical antipsychotic agent.

25 57. The method of any one of claims 41 through 53 wherein the dopamine D₂ receptor antagonist is effective for treating schizophrenia.

58. The method of any one of claims 41 through 53 wherein the D₁ dopamine receptor agonist and the D₂ dopamine receptor antagonist are administered to the patient in the same composition.

30 59. The method of any one of claims 41 through 53 wherein the D₁ dopamine receptor agonist and the D₂ dopamine receptor antagonist are administered to the patient in different compositions.

60. The method of any one of claims 41 through 53 wherein the D₁ dopamine receptor agonist is a full D₁ dopamine receptor agonist.

61. A method for treating a patient susceptible to or having a neurological, psychotic, or psychiatric disorder, said method comprising the steps of:
administering to the patient an effective amount of a dopamine D₁ receptor agonist; and administering to the patient an effective amount of a dopamine
5 D₂ receptor antagonist;
where the dopamine D₁ receptor agonist and the dopamine D₂ receptor antagonist are administered contemporaneously.

62. The method of claim 28 wherein the dopamine D₁ receptor agonist is a full agonist selected from the group consisting of
10 hexahydrobenzophenanthridines, hexahydrothienophenanthridines, chromenoisoquinolines, naphthoisoquinolines, analogs and derivatives thereof, pharmaceutically acceptable salts thereof, and combinations thereof.